



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 74

[Docket No. FDA-2011-C-0050]

D&C Red No. 6 and D&C Red No. 7; Change in Specification

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is revising its requirements for D&C Red No. 6 and D&C Red No. 7 by replacing the current specification for “Ether-soluble matter” with a maximum limit of 0.015 percent for the recently identified impurity 1-[(4-methylphenyl)azo]-2-naphthalenol. This action is in response to a petition filed by Sun Chemical Corp.

DATES: This rule is effective August 7, 2012, except as to any provisions that may be stayed by the filing of proper objections. Submit either electronic or written objections and requests for a hearing by August 6, 2012. See section XI of this document for information on the filing of objections.

ADDRESSES: You may submit objections and requests for a hearing, identified by Docket No. FDA-2011-C-0050, by any of the following methods:

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written objections in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2011-C-0050 for this rulemaking. All objections received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For detailed instructions on submitting objections, see section XI of this document.

Docket: For access to the docket to read background documents or objections received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

In a notice published in the Federal Register of April 14, 2011 (76 FR 20992), FDA announced that Sun Chemical Corp., 5020 Spring Grove Ave., Cincinnati, OH 45232, had filed a color additive petition (CAP 1C0290) requesting that FDA amend its regulations for D&C Red No. 6 and D&C Red No. 7 by replacing the current specification for “Ether-soluble matter” with a maximum limit of 0.015 percent for the recently identified impurity 1-[(4-methylphenyl)azo]-2-naphthalenol. As part of CAP 1C0290, Sun Chemical Corp. also requested that FDA remove Appendix A in part 74 (21 CFR part 74), which pertains to the ether-soluble matter specification.

D&C Red No. 6 and D&C Red No. 7 are principally monosulfo monoazo dyes prepared by the coupling of diazotized 2-amino-5-methylbenzenesulfonic acid with 3-hydroxy-2-naphthalenecarboxylic acid in alkaline medium. D&C Red No. 6 is produced as the disodium salt, whereas D&C Red No. 7 is the corresponding monocalcium salt. D&C Red No. 6 is listed in § 74.1306 for use in coloring drugs and in § 74.2306 for use in coloring cosmetics. D&C Red No. 7 is listed in § 74.1307 for use in coloring drugs and in § 74.2307 for use in coloring cosmetics. The identity and specifications in §§ 74.1306 and 74.1307 are referenced by §§ 74.2306 and 74.2307. Both color additives are required to be batch certified by FDA before they may legally be used in drugs and cosmetics marketed in the United States.

II. Regulatory History

In the Federal Register of December 28, 1982 (47 FR 57681), FDA published a final rule that permanently listed D&C Red No. 6 and D&C Red No. 7 for use in coloring drugs and cosmetics. The final rule described how D&C Red Nos. 6 and 7 contained ether-soluble matter for which the proponents of the color additives were not able to determine the chemical identity. FDA’s final rule established a specification for ether-soluble matter for both color additives, determined by a pass/fail test described in Appendix A of part 74. In the specified test, ether-

soluble matter is extracted from each new sample submitted for batch certification and analyzed by visible spectrophotometry. As explained in the final rule, FDA determined that spectrophotometric analysis provided a means of measuring the ether-soluble matter that may be present in each batch. Appendix A includes a reference spectrum that was based on the D&C Red No. 6 lot (the D&C No. 6 reference lot) that was used for toxicology testing in support of the permanent listing of D&C Red No. 6 and D&C Red No. 7. The sample passes the test if the absorption spectrum of the analyte does not exceed the reference spectrum in Appendix A at any wavelength. The reference spectrum represents 150 percent of the ether-soluble matter in the D&C Red No. 6 reference lot. The test is not capable of further characterizing the analyte.

III. Petitioned Request

Sun Chemical Corp.'s petition is based on the recent identification of 1-[(4-methylphenyl)azo]-2-naphthalenol (CAS No. 6756-41-8), the uncarboxylated-unsulfonated homolog of the dye component, as the major component of the ether-soluble matter. The identity of the ether-soluble matter was confirmed by FDA using liquid chromatography/mass spectrometry (LC/MS) (Ref. 1). As part of this work, FDA chemists prepared and characterized a reference standard for 1-[(4-methylphenyl)azo]-2-naphthalenol for LC analysis (Ref. 1). FDA chemists also determined that the D&C Red No. 6 reference lot, which was used as the reference for Appendix A, contains 0.0099 percent of 1-[(4-methylphenyl)azo]-2-naphthalenol (Ref. 1).

In its petition, Sun Chemical Corp. notes that the spectrum in Appendix A of part 74 represents 150 percent of the ether-soluble matter in the lot that was used as the reference for the appendix, and that this lot was found to contain 0.0099 percent of 1-[(4-methylphenyl)azo]-2-naphthalenol. Based on this finding, the company notes that the pass test result (150 percent) of 0.0099 percent is 0.015 percent and that 0.015 percent therefore corresponds to the maximum

amount of ether-soluble matter permitted in D&C Red Nos. 6 and 7. Accordingly, Sun Chemical Corp. requests 0.015 percent as the specification limit for 1-[(4-methylphenyl)azo]-2-naphthalenol. In addition, Sun Chemical Corp. requests that Appendix A be removed from part 74 and asks that the specification for ether-soluble matter in §§ 74.1306 and 74.1307 (which refers to the pass test in Appendix A) be replaced.

IV. Exposure Evaluation

In the final rule permanently listing D&C Red No. 6 and D&C Red No. 7, the acute cumulative exposure to these color additives was calculated to be 8 milligrams per person per day (mg/p/d), and the chronic exposure was calculated to be 2 mg/p/d (47 FR 57681 at 57685). These estimates have not changed as a result of the subject petition because both D&C Red No. 6 and D&C Red No. 7 are intended to be used in the same manner as currently permitted. In addition, the maximum amounts of ether-soluble matter permitted in D&C Red Nos. 6 and 7 have not changed, as the proposed specification limit, 0.015 percent, corresponds to the pass test result in Appendix A (150 percent of 0.0099 percent is 0.015 percent). Based on the petitioner's proposed specification limit of 0.015 percent and the exposure to D&C Red Nos. 6 and 7 from their regulated uses, FDA determined that the short-term (acute) exposure would be no greater than 1.2 micrograms per person per day ($\mu\text{g/p/d}$), and the lifetime average (chronic) exposure to this impurity would be no greater than 0.3 $\mu\text{g/p/d}$. FDA concludes that no increase in exposure to 1-[(4-methylphenyl)azo]-2-naphthalenol is expected as a result of the proposed changes to §§ 74.1306, 74.1307, 74.2306, and 74.2307 because the maximum amount of this impurity permitted in the color additives has not changed (Ref. 2).

FDA also notes that it conducted a survey of the amounts of 1-[(4-methylphenyl)azo]-2-naphthalenol in D&C Red No. 6 and D&C Red No. 7 straight colors and lakes. In addition to

analyzing the D&C Red No. 6 reference lot discussed earlier, FDA analyzed 25 other lots: 4 other lots of D&C Red No. 6, 4 lots of D&C Red No. 7, 8 lots of D&C Red No. 6 lake, and 9 lots of D&C Red No. 7 lake. Of these 25 other lots, only 3 contained detectable amounts of the impurity, specifically, 0.0006 percent, 0.0008 percent, and 0.002 percent (Ref. 1). FDA also analyzed for 1-[(4-methylphenyl)azo]-2-naphthalenol in samples of D&C Red No. 6 and D&C Red No. 7 submitted for batch certification between July 2009 and January 2011. Sixty-four samples of D&C Red Nos. 6 and 7 from eight domestic and foreign manufacturers were analyzed by LC for the impurity. All of the results obtained were well below 0.015 percent, and the average amount found, 0.0016 percent, is nearly an order of magnitude lower than the petitioned specification limit (Ref. 3).

V. Safety Evaluation

Under section 721(b)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379e(b)(4)), a color additive may not be listed for a particular use unless a fair evaluation of the data and information available to FDA establishes that the color additive is safe for that use. FDA's color additive regulations at 21 CFR 70.3(i) define safe as the existence of "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive." Numerous toxicology studies on D&C Red Nos. 6 and 7 were performed to support their permanent listing (47 FR 57681). The color additives tested contained the ether-soluble matter, now identified as primarily 1-[(4-methylphenyl)azo]-2-naphthalenol. Based on the results from these studies, the Agency concluded that D&C Red Nos. 6 and 7 (including the ether-soluble matter as determined by the test described in Appendix A) for use in drugs and cosmetics, excluding use in the area of the eye (47 FR 57681 at 57686), is safe. Therefore, although the chemical identity of the principal component of the ether-soluble matter

(i.e., 1-[(4-methylphenyl)azo]-2-naphthalenol) was not known when D&C Red Nos. 6 and 7 were permanently listed, the safety of the color additives, which contained the unknown ether-soluble matter, was assessed by FDA through the results of toxicological testing of the color additives containing this impurity.

The requested revision would not change the composition of D&C Red No. 6 or D&C Red No. 7 specified in the applicable color additive regulations, including the permissible level of the impurity. Nor would it change the authorized intended use. Therefore, the Agency concludes that the proposed revision would not affect FDA's safety evaluation in the final rule listing D&C Red No. 6 or D&C Red No. 7. Because there is no increase in the intake of the impurity or of D&C Red No. 6 and D&C Red No. 7 beyond a level that has already been established as safe, FDA has no safety concerns regarding the petitioned revision.

VI. Proposed Removal of Appendix A

FDA will no longer analyze the impurity by visible spectrophotometry when new samples of the color additive are submitted for batch certification. Instead, FDA will test the impurity using reversed-phase high performance liquid chromatography and will continue to do so for as long as the Agency determines that reversed-phase high performance liquid chromatography is appropriate. Because Appendix A of part 74 describes the spectrophotometry test for the ether-soluble matter, and because FDA will no longer analyze the impurity using spectrophotometry, FDA agrees with Sun Chemical Corp.'s request that Appendix A be removed from part 74.

VII. Conclusion

FDA reviewed data in the petition from Sun Chemical Corp. and other relevant data and information to evaluate the safety of revising its requirements for D&C Red Nos. 6 and 7 by

replacing the current specification for ether-soluble matter with a maximum limit of 0.015 percent for the impurity 1-[(4-methylphenyl)azo]-2-naphthalenol and by removing Appendix A in part 74, which pertains to the ether-soluble matter specification. Based on this information, the Agency does not have any safety concerns with the proposed amendment and concludes that D&C Red Nos. 6 and 7 will continue to be safe and suitable for their listed uses in drugs and in cosmetics. Therefore, the regulations in part 74 should be amended as set forth in this document. In addition, FDA will no longer analyze the impurity by visible spectrophotometry when new samples of the color additive are submitted for batch certification. Instead, FDA will test the impurity using reversed-phase high performance liquid chromatography.

VIII. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition will be made available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person (see FOR FURTHER INFORMATION CONTACT). As provided in § 71.15, the Agency will delete from the documents any material that is not available for public disclosure before making the documents available for inspection.

IX. Environmental Impact

The Agency has previously considered the environmental effects of this rule as announced in the notice of filing for CAP 1C0290 (76 FR 20992). No new information or comments have been received that would affect the Agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required.

X. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XI. Objections

This rule is effective as shown in the DATES section of this document; except as to any provisions that may be stayed by the filing of proper objections. Any person who will be adversely affected by this regulation may file with the Division of Dockets Management (see ADDRESSES) either electronic or written objections. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the Agency has received or lack thereof in the Federal Register.

XII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. B.P. Harp, A.L. Scher, H.-H.W. Yang, et al., “Reversed-Phase LC Determination of Two Manufacturing Intermediates, the Unsulfonated Subsidiary Color, and 4-Methyl-Sudan I in D&C Red No. 6, D&C Red No. 7, and Their Lakes,” Journal of AOAC International, vol. 92, pp. 888-895, 2009.

2. Memorandum to the file, CAP 1C0290 from H. Lee, FDA to T. Croce, FDA dated February 23, 2011.

3. Memorandum to the file, CAP 1C0290 from B. Harp, FDA to T. Croce, FDA dated April 18, 2011.

List of Subjects in 21 CFR Part 74

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 74 is amended as follows:

PART 74--LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for 21 CFR part 74 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Section 74.1306 is amended by removing the entry for “Ether-soluble matter” in paragraph (b) and adding in its place a specification for “1-[(4-methylphenyl)azo]-2-naphthalenol” to read as follows:

§ 74.1306 D&C Red No. 6.

* * * * *

(b)* * *

1-[(4-methylphenyl)azo]-2-naphthalenol, not more than 0.015 percent.

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3. Section 74.1307 is amended by removing the entry for “Ether-soluble matter” in paragraph (b) and adding in its place a specification for “1-[(4-methylphenyl)azo]-2-naphthalenol” to read as follows:

§ 74.1307 D&C Red No. 7.

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(b)* * *

1-[(4-methylphenyl)azo]-2-naphthalenol, not more than 0.015 percent.

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4. Part 74 is amended by removing Appendix A to Part 74--The Procedure for Determining Ether Soluble Material in D&C Red Nos. 6 and 7.

Dated: June 29, 2012.

Dennis M. Keefe,

Director,

Office of Food Additive Safety,

Center for Food Safety and Applied Nutrition.

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